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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/546,139	CHATEAU ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/11/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,14 and 44-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,14 and 44-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/11/2009 has been entered.

Claim Status

Claims 13-14 and 44-49 are pending. Claims 13-14 and 44-49 are amended. Claims 1-12 and 15-42 are cancelled. Claims 13-14 and 44-49 are under current examination.

Priority

This application claims benefit as a 371 of PCT/FR04/00354 (filed 02/17/2004), which claims foreign priority from foreign patent applications, FRANCE 03/13054 (filed 11/6/2003) and FRANCE 03/05769 (filed 5/14/2003) and FRANCE 03/05768 (filed 5/14/2003) and FRANCE 03/01924 (filed 2/18/2003). The instant application has been granted the benefit date, 18 February 2003, from the application FRANCE 03/01924.

RESPONSE TO ARGUMENTS

Claim Objections

The objection to claim 42 as being a substantial duplicate of claim 41 is withdrawn because of the applicant's amendment. Claims 41-42 have been cancelled.

35 USC § 103

The rejection of claims 13-14, 38-41 and 43-49 under 35 U.S.C. 103(a) as being obvious over unpatentable over Richaud et al. (J. Biological Chemistry. December 25, 1993; 268(36):26827-26835) in view of Short et al. (US2005/0124010, published June 19, 2005) is withdrawn in response to the applicants claim amendments.

The applicant's claim amendments have been fully considered and are persuasive. The applicant has amended the claims to recited that the evolved protein is made in a microorganism having a disrupted *metE* gene. The cited art (Richaud and Short) does not teach this limitation.

Therefore, the examiner hereby withdraws the rejection of claims 13-14, 38-41 and 43-49 under 35 U.S.C. 103(a) as being obvious over unpatentable over Richaud et al. in view of Short et al.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13-14 and 44-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richaud et al. (J. Biological Chemistry. December 25, 1993; 268(36):26827-26835) in view of Schroder et al. (US2008/0118959) and further in view of Thanbichler et al. (Journal of Bacteriology. Jan 1999; 181(2): 662-665).

Claim 13 is directed to a method for the producing an evolved protein involved in methionine biosynthesis pathway, the method comprising: a) disrupting metE gene in an initial microorganism to yield a modified microorganism, wherein the ability of the modified microorganism to grow is impaired when the modified microorganism is grown on a minimal medium containing no methionine, S-adenosylmethionine, homocysteine, or cysathionine; b) culturing the modified microorganism obtained in step (a) on the minimal medium for multiple generations, under selection pressure in the presence of methylmercaptan, allowing the modified microorganism to evolve a metabolic pathway; c) selecting an evolved microorganism from step (b) able to grow on the minimal medium, wherein at least one protein has evolved in the methionine biosynthesis pathway allowing the modified microorganism to produce methionine and proliferate; d) isolating the evolved protein.

The specification defines an evolved protein as "a sequence of amino acids (protein sequence) that differs in at least one amino acid from the initial protein sequence after selection" (page 4, lines 5-8). According to the specification, selection is defined as "a culture method used to select microorganisms that have evolved in such a way that a modification does not affect growth anymore" (page 3, lines 22-24). The

specification does not explicitly define the phrase "directed genetic modification." Accordingly, the examiner will interpret these terms broadly.

Richaud et al. broadly teach a method for producing an evolved protein involved in methionine biosynthesis pathway, comprising most of the steps set forth in the instant claims, except that rather than disrupting the *metE* gene, as in the instant claims, Richaud et al. disrupt the *metC* gene. Accordingly, Richaud and the instant claims are both species of a broader genus of methods of modifying genes of the methionine biosynthesis pathway, using a protein evolution strategy. The details of Richaud are elaborated below.

In addition, Schroder et al. teach a method for producing sulfur-containing fine chemicals, such as methionine, comprising most of the steps set forth in the instant claims, except that rather than disrupting the *metE* gene, as in the instant claims, Schroder et al. disrupt the *metK* gene. Furthermore, Schroder et al. teach that the *metE* gene is an important enzyme involved in the synthesis of methionine which can be studied during the method of producing methionine (parag.0009). The teachings of Schroder et al. are elaborated below.

Richaud et al. teach a very similar method as that of the instant claims. Richaud et al. teach "disrupting the metC gene" (abstract) of *E. coli*, which the examiner interprets as satisfying the general limitations directed to "generating a directed genetic modification in a gene of interest in an initial microorganism," as described in part a) of claim 13. Richaud et al. teach "a latent metabolite could under certain circumstances fulfill an essential need in cell chemistry, the way would be open for establishing a

biosynthetic pathway *de novo*" (page 26827, col.1), which satisfies the limitations of part b) claim 13, directed to evolution of a metabolic pathway. Richaud et al. culturing the mutant microorganism in minimal medium. Richaud et al. also teach "techniques of metabolic engineering can be applied to evolving the chemical constitution of living cells beyond its present state" (abstract), which is similar to the broad outline of the instant invention provided by the specification. Furthermore, Richaud et al. teach "a metC mutation enhances the growth of *dap* strains exogenously supplied with L-lanthionine, meso-lanthionine, or L-allo-cystathionine as the cross-linking amino acid' and is absolutely required for growing such strains with exogenous L-cystathionine (Table VI). The broad activity of cystathionase, which is indeed known to degrade generically L-cysteine thioethers in vitro, can thus be rationalized as fulfilling a corrective task, which adds to the biosynthetic function of the enzyme in E. coli metabolism " (page 26834, col.1, parag.1), which the examiner interprets as satisfying the limitations of part a) and b) of claim 13, directed to "wherein the production or consumption of a substrate is inhibited when the modified microorganism is grown on a defined medium, wherein the ability of the modified microorganisms to grow is impaired" and "wherein the defined medium can contain a co-substrate." Richaud et al. further indicate, [t]hese strains can thus be viewed as having undergone an evolutionary commitment to use cysteine thioethers for building their cell wall. Although this commitment did not result from natural selection but was rationally set up in their genome, the fitness of the committed strains might now be improved by natural selection" (page 26834, col.2, parag.1).

Richaud et al. do not teach: (1) disruption of *metE*, (2) isolation of the evolved protein and (3) growing the microorganism in minimal medium with methylmercaptan as a sulfur source.

The instant claims share a basic scheme common to classical microbial genetics. Schroder et al. teach the basic idea used in the instant claims: "mutagenesis, selection, and choice of mutants" (parag.0004). Schroder et al. teach deletion of *metK* gene in bacteria. Schroder teach culturing and fermentation of a methionine-producing microorganism with a reduced metK activity (parag.0071). Schroder teach growing the microorganisms in minimal medium with mercaptans as a sulfur source (parag.0235) for multiple generations (parag.0229). Schroder et al. teach protein extracts prepared from cultured cells Finally, Schroder et al suggest that metE and closely related metH are important enzymes involved in the synthesis of methionine which can be studied during the method of producing methionine.

Schroder et al. do not explicitly teach disruption of *metE.*

Thanbichler et al. teach the importance of *metE* and *metH* in the synthesis of methionine. Furthermore, Thanbichler et al. teach studying an *E. coli* mutant having a deletion of the *metE* gene for its involvement in alternative pathways of producing methionine.

Richaud et al. and Schroder et al. teach the basic concepts of claims 44-49.

Claim 44 is directed to the method of claim 13, wherein the genetic modification comprises the directed mutation or deletion of a gene of interest or the directed modification of a promoter in the gene of interest. Richaud et al. teach "disrupting the

metC gene" (abstract) of *E. coli*, which the examiner interprets as satisfying the limitations directed to "generating a directed genetic modification in a gene of interest in an initial microorganism," as described in part a) of claim 13. Likewise, Schroder et al. teach deletion of a gene involved in methionine synthesis, metK.

Claim 45 is directed to the method of claim 13, wherein the genetic modification consists in the removal of most of the gene of interest. Richaud et al. teach "disrupting the metC gene" (abstract) of *E. coli*, which the examiner interprets as satisfying the limitations directed to "generating a directed genetic modification in a gene of interest in an initial microorganism," as described in part a) of claim 13. The type of mutation does not seem to be particularly important to the practice of the method. Any type of null mutant, whether created by a deletion, point mutation, etc would be obvious in light of the teachings of Richaud et al. Likewise, Schroder et al. teach deletion of a gene involved in methionine synthesis, metK.

Claim 46 is directed to the method of claim 13, wherein the gene of interest is replaced with a selection marker gene. The type of mutation does not seem to be particularly important to the practice of the method. Any type of null mutant, whether created by a knockout by replacing the gene of interest with a selection marker, or by any other known means, would be obvious in light of the teachings of Richaud et al.

Claim 47 is directed to the method of claim 13, wherein the microorganism is a bacteria. Richaud et al. teach a method which uses *E. coli*. Schroder et al. and Thanbichler et al. teach bacteria.

Claim 48 is directed to the method of claim 13, wherein the microorganism is a *Escherichia sp.* Richaud et al. teach a method which uses *Escherichia coli.* Schroder and Thanbichler teach *Escherichia coli.*

Claim 49 is directed to the method of claim 13, wherein the microorganism is *E. coli* and *C. glutamicum.* The instant specification does not describe a method that uses two different microorganisms, so the examiner is interpreting the instant claim as reciting "or" rather than "and." In particular, the specification describes using either *E. coli* or *C. glutamicum* on page 8, lines 8-10 of the specification. Richaud et al. and Schroder et al. and Thanbichler et al. teach methods which use *E. coli.*

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Richaud et al and Shroder et al. and Thanbichler et al. so that the metE gene is disrupted and a method of protein evolution is practiced such that an evolved protein produced by the microorganisms of can be isolated and methionine is produced.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (methods of protein evolution; importance of *metE* in methionine biosynthesis) is taught by Richaud or Shroder or Thanbichler and further they are taught in various combinations and are shown to be immunogenic or used as vaccines. It

would be therefore predictably obvious to use a combination of these elements in a method of producing an evolved protein during methionine biosynthesis. The combined teachings suggesting substituting *metE* in the methods of Richard and Schroder.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Richaud et al. and Shroder et al. and Thanbichler et al. because these teachings generated evolved microorganisms and discuss the proteins which make possible the growth of the auxotrophic organisms.

Therefore the method as taught by Richaud et al. in view of Shroder et al. and further in view of Thanbichler would have been *prima facie* obvious over the method of the instant application.

Conclusion

No claims allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Scott Long/
Examiner, Art Unit 1633